

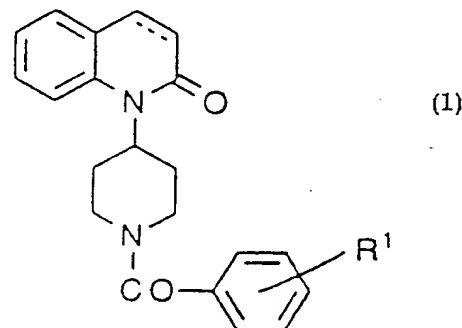
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(54) Title: AGENT FOR PROPHYLAXIS OR TREATMENT OF CATARACT

(57) Abstract

An agent for prophylaxis or treatment of cataract, which comprises as an active ingredient at least one compound selected from a group consisting of a carbostyryl compound of formula (1), wherein R¹ is a lower alkanoyl-substituted lower alkoxy group, and the bond between the 3- and 4-positions of the carbostyryl nucleus is single bond or double bond, or a salt thereof, 5-dimethylamino-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-benzazepine and hydroxy-7-chloro-1-[2-methyl-4-(2-methyl-benzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-benzazepine, a method for prophylaxis or treatment of cataract using the same.



DESCRIPTION

AGENT FOR PROPHYLAXIS OR TREATMENT OF CATARACT

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Technical Field

The present invention relates to an agent for prophylaxis or treatment of cataract comprising as an active ingredient a specific carbostyryl compound or benzazepine compound, and a method for prophylaxis or treatment of cataract by using the same.

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Background Art

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The carbostyryl and benzazepine compounds used as an active ingredient in this invention have already been known. For example, the carbostyryl compounds are disclosed in European Patent Publication No. 0382185 (published on August 15, 1990) and U.S. Patent No. 5,225,402 (issued on July 6, 1993), wherein it is disclosed that these compounds have vasopressin antagonistic activities and are useful as vasodilator, hypotensive agent, water diuretics, and platelet aggregation inhibitor. The benzazepine compounds are disclosed in WO 91/05549 (published on May 2, 1991) and U.S. Patent 5,258,510 (issued on November 2, 1993), wherein it is disclosed that the compounds have vasopressin antagonistic activities and are useful as vasodilator, hypotensive agent, water diuretics, and platelet aggregation inhibitor. However, it has never been known that the specific carbostyryl and benzazepine compounds are effective for the prophylaxis or treatment of cataract.

The present inventors have intensively studied in order to develop a novel agent for prophylaxis or treatment of cataract,

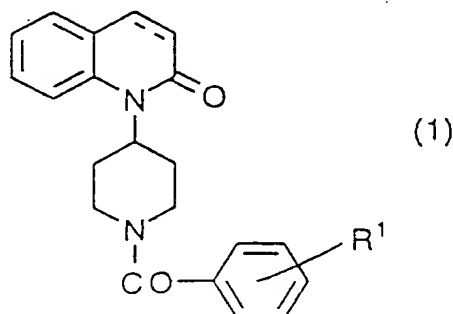
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and a novel method for prophylaxis or treatment of cataract, and have found that some specific carbostyryl compounds and benzazepine compounds are useful in the prophylaxis or treatment of cataract.

5 Cataract means the condition of the crystalline lens which loses the transparency thereof by storage of water in lens fiber and between lens fibers, or the mass caused by the coagulation of protein, and includes, for example, congenital cataract, or acquired cataracts such as senile cataract, anterior subcapsular
10 cataract, posterior subcapsular cataract, diabetic cataract, cataract accompanying with muscular rigiditic atrophy, irradiation cataract, cataract owing to siderosis, Down's syndrome cataract, Christmas-tree cataract, and the like. Although there are many theories concerning factors causing cataract, for example, disorder
15 in crystalline lens, changes of transparency of lens capsule and lens epithelial, change in ciliary epithelial, i.e. change in chamber water, and the like, it has not been proved yet.

Disclosure of the Invention

20 An agent for prophylaxis or treatment of cataract of the present invention comprises as an active ingredient at least one of the compounds selected from a group consisting of a carbostyryl compound of the formula:



wherein R^1 is a lower alkanoyl-substituted lower alkoxy group, and the bond between the 3- and 4-positions of the carbostyrl nucleus is single bond or double bond, a salt thereof, 5-dimethylamino-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-benzazepine and 5-hydroxy-7-chloro-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-benzazepine.

The "lower alkanoyl-substituted lower alkoxy group" in the above formula (1) includes a straight chain or branched chain alkoxy group having 1 to 6 carbon atoms which is substituted by a straight chain or branched chain alkanoyl group having 1 to 6 carbon atoms, for example, acetylaminomethoxy, 2-(formylamino)ethoxy, 1-(propionylamino)ethoxy, 3-(butyrylamino)propoxy, 3-(acetylaminopropoxy, 4-(isobutyrylamino)butoxy, 5-(pentanoylamino)pentyloxy, 6-(hexanoylamino)hexyloxy, and the like.

Among the active compounds (1) of the present invention, the compounds (1) having an acidic group can easily be converted into salts by treating with a pharmaceutically acceptable basic compound. The basic compound includes, for example, alkali metal or alkaline earth metal hydroxides (e.g. sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide, etc.), alkali metal carbonates or hydrogen carbonates (e.g. sodium carbonate, sodium hydrogen carbonate, etc.), and alkali metal alcoholates (e.g. sodium methylate, potassium methylate, etc.).

Besides, among the active compounds (1) of the present invention, the compounds having a basic group can easily be converted into acid addition salts by treating with a pharmaceutically acceptable acid. The acid includes, for example, inorganic acids (e.g. sulfuric acid, nitric acid, hydrochloric acid, hydrobromic acid, etc.), and

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organic acids (e.g. acetic acid, p-toluenesulfonic acid, ethane-sulfonic acid, oxalic acid, maleic acid, citric acid, succinic acid, benzoic acid, etc.). These salts are also useful in the prophylaxis or treatment of cataract as the active compounds (1).

5 The active compounds of the present invention show inhibitory activity of development of cataract without decreasing the blood glucose concentration in cataract model produced by streptozotocine (STZ). Thus, the agent of the active compounds of the present invention is useful for the prophylaxis or treatment of
10 various congenital cataract and acquired cataract.

 The agent for prophylaxis or treatment of cataract of the present invention are used in the form of a conventional pharmaceutical preparation. The pharmaceutical preparation is prepared by using conventional diluents or carriers such as fillers,
15 thickening agents, binders, wetting agents, disintegrators, surfactants, lubricants, and the like. The pharmaceutical preparation may be selected from various forms in accordance with the desired utilities, and the representative forms are tablets, pills, powders, solutions, suspensions, emulsions, granules,
20 capsules, suppositories, injections (e.g. solutions, suspensions, etc.), ointments, eye drops, and the like.

 In order to form in tablets, there are used conventional carriers such as vehicles (e.g. lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline
25 cellulose, silicic acid, etc.), binders (e.g. water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethyl cellulose, shellac, methyl cellulose, potassium phosphate, polyvinylpyrrolidone, etc.), disintegrators (e.g. dry

starch, sodium alginate, agar powder, laminaran powder, sodium hydrogen carbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium laurylsulfate, stearate monoglyceride, starches, lactose, etc.), disintegration inhibitors (e.g. white sugar, stearin, cacao butter, hydrogenated oil, etc.), absorption promoters (e.g. quaternary ammonium base, sodium laurylsulfate, etc.), wetting agents (e.g. glycerin, starches, etc.), adsorbents (e.g. starches, lactose, kaolin, bentonite, colloidal silicates, etc.), lubricants (e.g. purified talc, stearates, boric acid powder, polyethylene glycol, etc), and the like. The tablets may optionally be in the form of a conventional coated tablet, such as sugar-coated tablets, gelatin-coated tablets, enteric coating tablets, film coating tablets, or double or multiple layer tablets.

In the preparation of pills, the carriers include vehicles (e.g. glucose, lactose, starches, cacao butter, hydrogenated vegetable oil, kaolin, talc, etc.), binders (e.g. gum arabic power, tragacanth powder, gelatin, ethanol, etc.), disintegrators (e.g. laminaran, agar, etc.), and the like.

Capsules may be prepared by charging a mixture of the active compound of the present invention and the above carriers into hard gelatin capsules or soft capsules in usual manner.

In the preparation of injections, the solutions, emulsions and suspensions are sterilized and are preferably made isotonic with the blood. In the preparation of these solutions, emulsions and suspensions, there are used conventional diluents, such as water, ethyl alcohol, macrogol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, polyoxyethylene sorbitan fatty acid esters, and the like. In this

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case, the pharmaceutical preparations may also be incorporated with sodium chloride, glucose or glycerin in an amount sufficient to make them isotonic, and may also be incorporated with conventional solubilizers, buffers, anesthetizing agents.

5 In the preparation of suppositories, the carriers include, for example, polyethylene glycol, cacao butter, higher alcohols, higher alcohol esters, gelatin, semi-synthetic glycerides, etc.), and the like.

10 The present eye drops may be prepared by a conventional manner. For example, the present eye drops may be prepared by incorporating the active compound of the present invention into a suitable base, and sterilized. The base includes, for example, sterile purified water.

15 The present eye drops may contain, if necessary, solubilizer, buffering agent, antioxidant, antiseptic, isotonicity, pH adjuster, and the like. The solubilizer is, for example, sodium carboxymethyl cellulose, polyethylene glycol ethers (e.g. polyoxyethylene lauryl ether, polyoxyethylene oleyl ether), polyethyleneglycol higher fatty acid esters (e.g. polyethylene glycol monolaurate, polyethylene glycol monooleate), polyoxyethylene ether fatty acid esters (e.g. polyoxyethylene sorbitan monolaurate), and the like. The buffering agent is, for example, sodium phosphate, dibasic sodium phosphate, dibasic potassium phosphate, boric acid, sodium borate, citric acid, sodium citrate, tartaric acid, sodium
20 tartrate, acetic acid, sodium acetate, ϵ -aminocaproic acid, monosodium glutamate, and the like. The antioxidant is, for example, sodium sulfite, sodium pyrosulfite, sodium bisulfite, sodium thiosulfite, ascorbic acid, and the like. The antiseptic is,

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for example, chlorobutanol, benzalkonium chloride, benzethonium chloride, phenyl mercury salt, thimerosal, phenethyl alcohol, methyl parabene, propyl parabene, and the like. The isotonicity is, for example, sodium chloride, glucose, D-mannitol, glycerin, and the like. The pH adjuster is, for example, sodium hydroxide, hydrochloric acid, and the like.

The present eye drops may be used in the same manner as conventional eye drops, for example, dropping into the eyes from a suitable eye dropper, or spraying onto the eyes with an atomizer.

Besides, the pharmaceutical preparations may optionally be incorporated with a coloring agent, preservatives, perfumes, flavors, sweetening agents, and other medicaments, if required. In the preparation of pastes, creams and gels, there are used conventional diluents, for example, white vaseline, paraffin, glycerin, cellulose derivatives, polyethylene glycol, silicone, bentonite, and the like.

The amount of the active compound of the present invention to be incorporated into the present agent for prophylaxis or treatment of cataract is not specified but may be selected from a broad range, but it is usually in the range of about 1 to 70 % by weight, more preferably about 5 to 50 % by weight, based on the total weight of the preparation.

The present agent for prophylaxis or treatment of cataract may be administered in any method, and suitable method for administration may be determined in accordance with various forms of preparations, ages, sexes and other conditions of the patients, the degree of severity of diseases to be cured, and the like. For example, tablets, pills, solutions, suspensions, emulsions,

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granules and capsules are administered orally. The injection are intravenously administered alone or together with a conventional auxiliary liquid (e.g. glucose, amino acid solutions), and further are optionally administered alone in intramuscular, intracutaneous, subcutaneous, or intraperitoneal route, if necessary. Suppositories are administered in intrarectal route. The ointment is applied on the skin.

The dosage of the present agent for prophylaxis or treatment of cataract may be selected in accordance with the administration routes, ages, sexes and other conditions of the patients, the degree of severity of diseases to be cured, and the like, but it may usually be in the range of about 0.6 to 50 mg of the active compound of the present invention per 1 kg of body weight of the patient per day. The active compound is preferably contained in an amount from about 10 to 1000 mg per the dosage unit.

Best Mode for Carrying Out the Invention

Examples

The present invention is illustrated in more detail by the following Preparations of agent for prophylaxis or treatment of cataract, and Experiment of the activities of the active compound of the present invention.

Preparation 1

Film coated tablets are prepared from the following components.

<u>Components</u>	<u>Amount</u>
1-{1-[4-(3-Acetylaminopropoxy)-benzoyl]-4-piperidinyl}-3,4-dihydrocarbostyrl	150 g
Avicel (trade name of microcrystalline cellulose,	

	manufactured by Asahi Chemical Industries, Co., Ltd.)	40 g
	Corn starch	30 g
	Magnesium stearate	2 g
	Hydroxypropyl methylcellulose	10 g
5	Polyethylene glycol-6000	3 g
	Castor oil	40 g
	Ethanol	40 g

10 The active compound of the present invention, Avicel, corn starch and magnesium stearate are mixed and kneaded, and the mixture is tabletted by using a conventional pounder (R 10 mm) for sugar coating. The tables thus obtained are coated with a film coating agent consisting of hydroxypropyl methylcellulose, polyethylene glycol-6000, castor oil and ethanol to give film coated tablets.

15 Preparation 2

Tablets are prepared from the following components.

	<u>Components</u>	<u>Amount</u>
	1-{1-[4-(3-acetylaminopropoxy)benzoyl]-4-piperidinyl}-3,4-dihydrocarbostyrl	150 g
		1.0 g
20	Citric acid	33.5 g
	Lactose	70.0 g
	Dicalcium phosphate	30.0 g
	Pluronic F-68	15.0 g
	Sodium laurylsulfate	15.0 g
25	Polyvinylpyrrolidone	4.5 g
	Polyethylene glycol (Carbowax 1500)	45.0 g
	Polyethylene glycol (Carbowax 6000)	30.0 g
	Corn starch	3.0 g
	Dry sodium stearate	

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Dry magnesium stearate	3.0 g
Ethanol	q.s.

The active compound of the present invention, citric acid, lactose, dicalcium phosphate, Pluronic F-68 and sodium laurylsulfate are mixed. The mixture is screened with No. 60 screen and is granulated with an alcohol solution containing polyvinylpyrrolidone, Carbowax 1500 and 6000. If required, an alcohol is added thereto so that the powder mixture is made a paste-like mass. Corn starch is added to the mixture and the mixture is continuously mixed to form uniform particles. The resulting particles are passed through No. 10 screen and entered into a tray and then dried in an oven at 100°C for 12 to 14 hours. The dried particles are screened with No. 16 screen and thereto are added dry sodium laurylsulfate and dry magnesium stearate, and the mixture is tabletted to form the desired shape.

The core tablets thus obtained are vanished and dusted with talc in order to guard from wetting. Undercoating is applied to the core tablets. In order to administer the tablets orally, the core tablets are vanished several times. In order to give round shape and smooth surface to the tablets, further undercoating and coating with lubricant are applied thereto. The tablets are further coated with a coloring agent material until the desired colored tablets are obtained. After drying, the coated tablets are polished to obtain the desired tablets having uniform gloss.

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Pharmacological Test

Test compound:

1. 1-{1-[4-(3-Acetylamino-propoxy)benzoyl]-4-piperidinyl}-3,4-dihydrocarbostyryl

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Method:

The left kidney of Wister male rat (weight; 280-330 g, 9 wk-old) was taken out under ether anesthetization. One week thereafter, a solution of streptozotocine (STZ) in 50 mM citric buffer (pH 4.5) was administered intravenously to the rats on the tail in an amount of 1 ml/kg (i.e. 60 mg of STZ/kg). After the administration of STZ, the rats are separated into two groups, and in one group, a test compound was orally administered to the rats by feeding the rats with feed containing a test compound (0.2 %). In another group, the rats were fed with the regular feed (MF) (control group B). Four weeks and 16 weeks after the administration of STZ, the blood glucose concentration in each rat was determined. The results are shown in Table 1.

A controlled-release preparation of insulin (Ultrarente) was administered every two days in an amount of 4 U/body, s.c. Sixteen weeks after the STZ administration, the crystalline lens of the rats were observed with the naked eyes, and if the crystalline lens was observed to be apparently cloud, it was determined to be cataract. The results are shown in Table 2.

Groups:

- | | |
|------------------|--|
| Control A: | Normal Wister rats having both kidneys administered with neither STZ nor test compound |
| Control B: | Wister rats having no left kidney administered with neither STZ nor test compound |
| Control C: | Wister rats having no left kidney administered with STZ but not with test compound |
| Test Compound 1: | Wister rats having no left kidney |

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administered with both STZ and Test
Compound 1

Table 1: Blood Glucose Concentration

Groups	After 4 weeks (mg/dl)	After 16 weeks (mg/dl)
Control A	131.4±6.3	133.4±8.5
Control B	126.0±4.0	125.4±10.1
Control C	775.8±41.1	670.4±28.1
Test Compound 1	801.6±37.9	728.9±40.0

Table 2:

Groups	Number of rats having cataract/ number of all rats in group
Control A	0/6
Control B	0/7
Control C	7/11*
Test Compound 1	1/10**

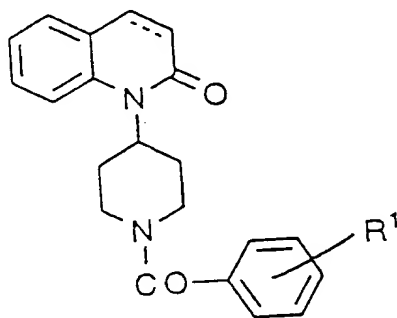
*: $p < 0.05$, Fisher Exact test

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 $p < 0.05$, Fisher Exact test
(based on the data of Control C and Test Compound 1)

As seen from the above data, when STZ alone was administered, the blood glucose level was increased and the cataract was observed in many test animals. On the other hand, the active compound of the present invention was also administered in addition to STZ, the blood glucose level was not decreased but rather increased, however, the cataract was significantly inhibited.

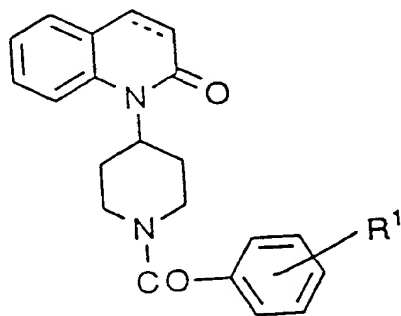
CLAIMS

1. An agent for prophylaxis or treatment of cataract, which comprises as an active ingredient at least one compound selected from a group consisting a carbostyryl compound of the formula:



wherein R¹ is a lower alkanoyl-substituted lower alkoxy group, and the bond between the 3- and 4-positions of the carbostyryl nucleus is single bond or double bond, a salt thereof, 5-dimethylamino-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-benzazepine and 5-hydroxy-7-chloro-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-benzazepine.

2. The agent for prophylaxis or treatment of cataract according to claim 1, wherein the active ingredient is a carbostyryl compound of the formula:



wherein R¹ is a lower alkanoyl-substituted lower alkoxy group, and the bond between the 3- and 4-positions of the carbostyryl nucleus

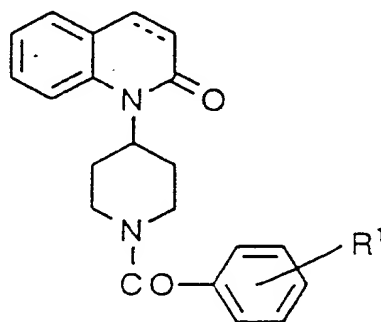
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is single bond or double bond, or a salt thereof.

3. The agent for prophylaxis or treatment of cataract according to claim 1, wherein the active ingredient is 5-dimethyl-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-benzazepine or 5-hydroxy-7-chloro-1-[2-methyl-4-(2-methyl-benzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-benzazepine.

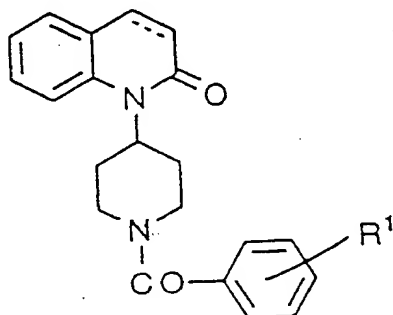
4. The agent for prophylaxis or treatment of cataract according to claim 2, wherein the active ingredient is 1-{1-[4-(3-acetylaminopropoxy)benzoyl]-4-piperidiny]-3,4-dihydrocarbostyryl or a salt thereof.

5. A method for prophylaxis or treatment of cataract, which comprises administering to a warm-blooded animal including a human being an agent for prophylaxis or treatment of cataract - which comprises as an active ingredient at least one compound selected from a group consisting of a carbostyryl compound of the formula:



wherein R¹ is a lower alkanoyl-substituted lower alkoxy group, and the bond between the 3- and 4-positions of the carbostyryl nucleus is single bond or double bond, a salt thereof, 5-dimethylamino-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-benzazepine and 5-hydroxy-7-chloro-1-[2-methyl-4-(2-methyl-benzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-benzazepine.

6. The method according to claim 5, which comprising administering the agent of claim 2 wherein the active ingredient is a carbostyrl compound of the formula:



10 wherein R¹ is a lower alkanoyl-substituted lower alkoxy group, and the bond between the 3- and 4-positions of the carbostyrl nucleus is single bond or double bond, or a salt thereof.

7. The method according to claim 5, wherein the active ingredient is 5-dimethyl-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-benzazepine or 5-hydroxy-7-chloro-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-benzazepine.

8. The method according to claim 6, wherein the active ingredient is 1-{1-[4-(3-acetylaminopropoxy)benzoyl]-4-piperidinyl}-3,4-dihydrocarbostyrl or a salt thereof.

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K31/47 A61K31/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 382 185 (OTSUKA PHARMACEUTICAL CO.) 16 August 1990 cited in the application	1,2,4
A	see abstract; claims 1,48; example 141 ---	5,6,8
X	CHEMICAL ABSTRACTS, vol. 116, no. 13, 30 March 1992, Columbus, Ohio, US; abstract no. 128686j, 'BENZOHETEROCYCLIC COMPOUNDS' cited in the application	1,3
A	see abstract & WO,A,91 05549 (OTSUKA PHARMACEUTICAL CO.) 2 May 1991 --- -/-	5,7



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- * "A" document defining the general state of the art which is not considered to be of particular relevance
- * "E" earlier document but published on or after the international filing date
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- * "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- * "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- * "&" document member of the same patent family

Date of the actual completion of the international search

27 April 1994

Date of mailing of the international search report

09.05.94

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 119, no. 23, 6 December 1993, Columbus, Ohio, US; abstract no. 249979c, 'PREPARATION OF N-BENZOYL BENZO-FUSED HETEROCYCLIC COMPOUNDS AS VASOPRESSIN ANTAGONISTS' see abstract	1,3
A	& JP,A,4 321 669 (OTSUKA PHARMACEUTICAL CO.) 11 November 1992 ---	5,7
X	THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS vol. 263, no. 2 , 1992 pages 627 - 631 Y. FURUKAWA ET AL. 'BLOCKING EFFECTS OF V1 (OPC-21268) AND V2 (OPC-31260) ANTAGONISTS ON THE NEGATIVE INOTROPIC RESPONSE TO VASOPRESSIN IN ISOLATED DOG HEART PREPARATIONS'	1-4
A	see the whole document ---	5-8
X	SCIENCE vol. 252, no. 5005 , 1991 pages 572 - 574 Y. YAMAMURA ET AL. 'OPC-21268, AN ORALLY EFFECTIVE, NONPEPTIDE VASOPRESSIN V1 RECEPTOR ANTAGONIST'	1,2,4
A	see the whole document -----	5,6,8

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WO-A-9105549	02-05-91	AU-B- 630284 AU-A- 7291791 EP-A- 0450097 US-A- 5258510 CN-A- 1051038 JP-A- 4154765	22-10-92 19-12-91 09-10-91 02-11-93 01-05-91 27-05-92
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